REMARKS/ARGUMENTS

I. Change of Attorney Docket No.:

At the outset, Applicants would like to remind the Examiner that the Attorney Docket No. for the instant application has changed. The new Attorney Docket No. for the instant application is **36119.156US3** as indicated in the caption on page 1.

Applicants respectfully request that the Attorney Docket No. be updated on PAIR, and that the new Attorney Docket No. be used in any future correspondence relating to the instant application.

II. Information Disclosure Statement:

Applicants gratefully note that the Examiner has fully considered the references cited in the PTO-1449 form mailed January 18, 2005.

III. Amendments to the Claims:

Claims 12-24 and 26-40 are pending in the instant application.

Claims 12-24 were withdrawn from consideration pursuant to 37 C.F.R. § 1.142(b). Applicants note that the Examiner had previously indicated that when the claims drawn to the product are allowable, the process claims (claims 12-24) would be rejoined (*see*, Office Action of July 30, 2004, page 2, first paragraph).

Claims 22, 26, 35 and 38-39 have been amended. Claims 22 and 35 have been amended to delete the recitation of "a hepatocarcinoma cell" in the Markush group of each of these claims. Claim 26 has been amended to insert the following claim terms: "isolated," "a first" and "a second" exogenous nucleic acid molecule. Claim 38 has been amended to add the phrase "inserted into," and claim 39 has been amended to correct the recitation of an improper claim dependency.

Claims 41-42 have been newly added. Support for the new claim 41 can be found in claim 35 prior to the instant amendment and throughout the application as filed. Support for new claim 42 can be found throughout the application as filed. Accordingly, no new matter has been added by way of the instant amendment to the claims.

Upon entry of the instant Amendment, claims 12-24 and 26-42 will be pending in this application.

IV. Rejections under 35 U.S.C. § 112, second paragraph:

Claims 35 and 39 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite (*see*, Office Action, page 3, third paragraph).

Specifically, with respect to claim 35, the Examiner argued that the recitation of "a mammalian cell" and "a hepatocarcinoma cell" renders the claim indefinite for allegedly not clearly setting forth the metes and bounds of the patent protection desired. Without acquiescing to this rejection, and solely in an effort to expedite prosecution, Applicants have amended claim 35 to delete reference to "a hepatocarcinoma cell." Accordingly, this rejection has been rendered moot.

With respect to claim 39, the Examiner stated that review of claims 20-38 does not reveal any claims drawn to "an expression vector." Claim 39 has been amended to recite, in relevant part, "[t]he cell of claim 38, wherein...". Accordingly, Applicants aver that this rejection has been overcome.

V. Rejections under 35 U.S.C. § 112, first paragraph:

(i) Claims 26-39 stand rejected under 35 U.S.C. § 112, first paragraph, for purportedly not being enabling for any host cell comprising the claimed exogenous nucleic acid molecules (*see*, Office Action, page 4, third paragraph).

The Examiner indicated that amending independent claim 26 to insert "isolated" before "cell" can obviate this rejection (*see*, Office Action, page 7, last paragraph). Following the Examiner's suggestion, Applicants have amended claim 26 to insert the claim term "isolated" before "cell." Accordingly, this rejection has been rendered moot.

(ii) Claims 26-40 were also rejected under 35 U.S.C. § 112, first paragraph, for purportedly introducing new matter (*see*, Office Action, page 8, first and second paragraphs).

Specifically, the Examiner alleged that the Office is not able to locate support in the disclosure for the three different components of independent claim 26 to be expressed from the same vector. Applicants respectfully direct the Examiner's attention to the paragraph bridging pages 4-5 of the specification. The last two sentences of this paragraph unambiguously provide such written description. Based on the foregoing, Applicants respectfully aver that the grounds for this rejection have been overcome.

VI. Rejections under 35 U.S.C. § 103(a):

(i) The Office Action rejected claims 26-27 and 30-40 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Calkhoven *et al.* (*Eur. J. Biochem.* **249**:113-120, 1997) in view of Ameis *et al.* (*J. Biol. Chem.* **265**:6552-6555, 1990), and further in view of Norris *et al.* (*J. Biol. Chem.* **270**:22777-22782, 1995) (*see,* Office Action, page 8, third paragraph).

According to the Office Action, the primary reference (*i.e.*, Calkhoven *et al.*) allegedly teaches HepG2 recombinant cells containing three DNA constructs, namely:

> (i) a DNA construct expressing an estrogen receptor;
>
> (ii) a DNA construct expressing a transcription coactivator C/EBP; and
>
> (iii) a reporter construct linking the CAT reporter gene to the apoVLDL II promoter (*see,* Office Action, page 9, first full paragraph).

The Office Action correctly notes that Calkhoven *et al.* do not teach a HL promoter or a luciferase reporter gene (*see,* Office Action, page 9, last paragraph).

The Office Action states that the secondary reference, Ameis *et al.*, purportedly teaches that the 5' untranslated region of the human HL gene contains two CCAAT elements, and also *Alu* DNA repeats (*see,* Office Action, page 10, first paragraph).

Finally, the Office Action alleges that Norris *et al.* teaches an *Alu* consensus sequence that binds ER, as well as an assay system using luciferase (*see,* Office Action, page 10, second paragraph).

The Office Action alleges that it would have been obvious to one of ordinary skill to make and use a recombinant cell containing the claimed DNA constructs with a reasonable expectation of success by replacing the apoVLDL II promoter of the reporter of Calkhoven *et al.*, with the HL promoter of Ameis *et al.* to arrive at an estrogen-dependent HL promoter-

driven reporter gene. The Office Action alleges that the skill in the art in making the claimed recombinant cell is very high and that one of ordinary skill would have been motivated to make and use an estrogen-dependent HL-promoter-driven reporter gene given that the *Alu* repeat of the HL promoter contains the consensus *Alu* sequence that binds ER as shown by Norris *et al.* (*see,* Office Action, paragraph spanning pages 10-11).

Applicants respectfully assert that the Office Action has failed to establish a *prima facie* case of obviousness for the reasons described below.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a), the Examiner must show that some objective teaching, suggestion, or motivation in the applied prior art taken as a whole and/or knowledge generally available to one of ordinary skill in the art would have led that person to the claimed invention as a whole, including each and every limitation of the claims, without recourse to the teaching in Applicants' disclosure. *See generally, In re Lee*, 277 F.3d 1338, 1343, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002); *In re Rouffett*, 149 F.3d 1350, 1358, 47 USPQ2d 1453, 1458 (Fed. Cir. 1998); and *In re Fritch*, 972 F.2d 1260, 1265-66, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992) (emphasis added).

The sole independent claim in the instant application, claim 26, recites an isolated cell comprising (i) a first exogenous nucleic acid molecule which encodes an estrogen receptor; (ii) a second exogenous nucleic acid molecule which encodes a CCAAT/enhancer-binding protein (C/EBP) transcription factor; and (iii) a reporter gene operatively associated with a hepatic lipase (HL) promoter.

As a preliminary matter, Applicants note that modifying Calkhoven's reporter construct as suggested by the Office Action would render Calkhoven's reporter unsatisfactory for its intended purpose. Calkhoven is interested in identifying the factors responsible for regulating the promoter region of the avian egg yolk precursor protein very low density apolipoprotein II (apoVLDL II). Thus, modifying Calkhoven's reporter by replacing the apoVLDL II promoter with the HL promoter would not in any way assist Calkhoven to achieve his desired goal. Applicants emphasize that Calkhoven shows no interest whatsoever in HL regulation. As the Examiner is aware, the Federal Circuit has made clear that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation

to make the proposed modification. *In re Gordon, 733 F.2d 900, 221 USPQ 1125* (Fed. Cir. 1984). Accordingly, Applicants respectfully assert that the Office Action has failed to establish a *prima facie* case of obviousness.

Adding to this deficiency, none of the three references cited by the Examiner, taken alone or in combination, teach or suggest Applicants' claimed invention with any expectation of success. Specifically, none of the references teach, suggest, or provide motivation for replacing the apoVLDL II promoter region in the apoVLDL-CAT reporter plasmid of Calkhoven with a hepatic lipase (HL) promoter of Ameis, or introducing exogenous nucleic acid molecules encoding ER and C/EBP transcription factors into an isolated cell having an HL reporter construct.

The Office Action has failed to identify any portion of Calkhoven that suggests the use of, or desirability of testing an HL reporter construct. The mere fact that Calkhoven's reporter can be modified to replace the apoVLDL II promoter with the HL promoter is insufficient to render Applicants' claimed invention obvious. The Federal Circuit has instructed that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills* 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Applicants further note that in contrast to the position of the Office Action, neither Ameis nor Norris provides any teaching, suggestion, or motivation to introduce an exogenous nucleic acid molecule encoding estrogen receptor (ER) and an exogenous nucleic acid molecule encoding C/EBP into an isolated cell containing a reporter gene driven by an HL promoter. Ameis *et al.* report that the human hepatic lipase gene 5'-nontranscribed region contains multiple cis-elements such as "TATA" box sequences, a hepatocyte-specific factor binding site "AGGTTAATTATTAAT," an element with homology to an "*Alu*" repeat sequence, two elements with homology to "CCAAT" elements, a cyclic AMP response element, and a glucocorticoid response element (*see*, Fig. 3 and page 6555, left column, first full paragraph).

To begin with, the mere identification of elements with homology to known binding sites is merely a first step in promoter analysis. That a cis-element with homology or identity to known transcription factor binding sites exists in an upstream non-transcribed

region, does not immediately imply that that site is bound by a transcription factor and/or that that site is involved in the functional regulation of the downstream gene. One of ordinary skill in the art would readily recognize that short cis-elements like TATA or CCAAT, have a high probability of appearing frequently in a sequence the size of the 5′ non-transcribed region of HL and that most of these occurrences would not correlate with functional activity. The role, if any, of any cis-elements with homology to known elements needs to be established by significant further experimentation. Such experimentation was done by the Examiner-cited reference, Calkhoven *et al.*, wherein DNAse I footprint studies and immune-EMSA's were performed to determine whether sites that were previously provisionally identified as binding sites for certain proteins are indeed capable of binding those proteins (*see,* page 115 right column to page 116). In addition, reporter studies need to be done to test whether the identified sites have any functional activity, as was done by Calkhoven *et al.* In the case of Ameis *et al.*, these authors do not test whether any transcription factors bind the reported cis-elements in the HL 5′ non-transcribed region and/or whether any of the cis-elements in the HL 5′ non-transcribed region of are functional. In other words, Ameis *et al.*, at best, serves as an invitation to experiment to identify factors, if any, that bind the elements with homologies to known cis-acting elements in the HL 5′ non-transcribed region and to test whether the binding of such factors correlates with transcriptional activity of this promoter.

Even if we assume *arguendo* that all of the cis-elements in the HL promoter/enhancer contribute to the regulation of the HL gene, none of the Examiner-cited references teach or suggest which proteins bind these different cis-elements. One of ordinary skill in the art at the time of the filing of the instant application would have been aware that a given cis-element can be recognized by more than one transcription factor. For example, at the time of the filing of the instant application, CCAAT sites were known to bind proteins other than C/EBP, such as NF-Y, CTF, CP1, and CDP. Thus, a protein that is distinct from C/EBP may bind the CCAAT elements in the HL 5′ non-transcribed region. The person of ordinary skill in the art would also be aware that the CCAAT element in the HL 5′ non-transcribed region may not bind any transcription factor (*i.e.*, it is a non-functional site). In the absence of further detailed promoter/enhancer analysis, one of ordinary skill in the art would have no

reason to conclude that C/EBP regulates the HL gene merely because the 5′ non-transcribed region contains CCAAT elements.

Even if *arguendo*, C/EBP were shown to bind the HL promoter/enhancer (which it is not), neither Ameis *et al.* nor any of the Examiner-cited references, teach or suggest that estrogen receptor be introduced along with C/EBP to regulate the HL promoter. Norris *et al.* merely teach that a certain class of *Alu* repeats when presented in the context of the pBL-TK-Luc reporter can function as ER-dependent enhancers. The fact that such an *Alu* repeat exists in the HL 5′ non-transcribed region provides no indication as to whether this element is regulated by ER in the context of the HL 5′ non-transcribed region. It is well known in the transcription field that the context of the target promoter is critical in determining which factors may bind to it and how they regulate that promoter. For example, if cis-elements A and B bind transcription factors X and Y in one promoter context, there is simply no certainty that the cis-elements A and B also bind X and Y when present in the context of a different regulatory region. Thus, Norris, at best, opens the door for further experimentation as to determining whether the *Alu* repeat in the HL 5′ non-transcribed region is regulated by ER.

In addition to the arguments made above, Applicants further note that there is simply no direction in any of the Examiner-cited references regarding which combination of transcription factors should be used to regulate the HL promoter. The fact that the HL promoter has CCAAT and *Alu* elements does not by itself, without more, lead one of ordinary skill in the art to choose the transcription factors which bind these elements. As detailed above, more than one factor can bind such elements, making the choice of transcription factor non-trivial. Furthermore, the Examiner has provided no rationale for why an ordinary skilled artisan would choose C/EBP and ER over any of the other possible combination of factors that may potentially regulate the HL gene. As the Examiner is aware, Ameis *et al.* teach that there are several cis-elements in the HL 5′ non-transcribed region. The Office Action has simply not provided any direction as to why ER and C/EBP would be chosen by one of ordinary skill in the art over any other possible combination.

The Federal Circuit has stated that:

> identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. Rather, to establish obviousness based on a combination of elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant." *In re Kotzab*, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000).

The Federal Circuit has also made clear that the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine prior art references. An adequate showing of motivation to combine requires "evidence that a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Ecolochem, Inc. v. Southern Calif. Edison Co.*, 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1075 (Fed. Cir. 2000). "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

For the reasons outlined above, Applicants respectfully contend that the Applicants' disclosure has been improperly used as a blueprint for piecing together the prior art to defeat patentability of Applicants' claimed invention.

Accordingly, Applicants respectfully assert that this rejection under 35 U.S.C. § 103(a) has been erroneously applied and respectfully request that it be reconsidered and withdrawn.

(ii) Claims 26-28 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Calkhoven *et al.* (*Eur. J. Biochem.* **249**:113-120, 1997) in view of Ameis *et al.* (*J. Biol. Chem.* **265**:6552-6555, 1990), further in view of Norris *et al.* (*J. Biol. Chem.* **270**:22777-22782, 1995), and further in view of Harnish *et al.* (*J. Biol. Chem.* **273**:9270-9278, 1998) (*see*, Office Action, page 12, first paragraph).

The Office Action relies on Calkhoven, Ameis, and Norris for the reasons described in the § 103(a) rejection above. Harnish is relied on to purportedly show that ERα or ERβ had been known before the effective filing date of the instant application (*see*, Office Action, page 12, third paragraph).

The Office Action alleges that it would have been obvious to one of ordinary skill in the art to make and use recombinant cells containing the three claimed DNA constructs with a reasonable expectation of success by using ERα or ERβ since one skilled in the art in making the claimed recombinant cell is very high (*see*, Office Action, page 12, fifth paragraph).

Applicants respectfully aver that Harnish does not remedy the multiple deficiencies of the other references detailed above. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

CONCLUSION

Claims 12-24 and 26-42 are pending in the instant application.

Applicants aver that all grounds of rejection have been overcome. Accordingly, Applicants respectfully request reconsideration and allowance of the claims of the instant application. If the Examiner believes that any further discussion of this communication would be helpful, the Examiner is encouraged to contact the undersigned at the phone number listed below.

No fees are believed to be due in connection with this communication. However, if any additional fees are due, please apply any additional charges, or credit any overpayment, to our Deposit Account No. 08-0219.

Respectfully submitted,

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